Fast and Sensitive Determination of Sulfur Dioxide in Herbal Medicines by Microchip-Based Field Asymmetric-wave Ion Mobility Spectrometry

Xiaozhi Wang [a*], Weijun Zhao[b], Juan Li[b], Lingfeng Li[a], Xiangyang Wang[a], Peng Li[c], Yu Wang[d*], Jikui Luo[a]

[a]*Department of Information Science & Electronic Engineering, Zhejiang University, Hangzhou 310027, China*

[b]*Su Zhou Wei Mu Intelligent System Ltd., Suzhou 215163, China*

[c] *Suzhou Industrial Technology Research Institute of Zhejiang University, Suzhou 215163, China*

[d] *Institute for Food and Drug Control of Jiangsu, Nanjing, 210008,China*

*** Corresponding author.**

Mailing address:

E- mail address: xw224@zju.edu.cn *(Xiaozhi Wang)*

Fax: +86-0571-87952257

E- mail address: yuwanga@hotmail.com *(Yu Wang)*

Fax: +86-025-86631982

ABSTRACT

Sulfites (SO_2) and inorganic sulfites are types of food additives and preservatives, widely used in food and herbal medicine (HMs) productions. However, over-taken of sulfites and its associates are harmful to human health and may cause medical complications. Various methods and instruments have been developed for measuring sulfites in foods and HMs with many shortages such as high detection limitation, inaccurate and non-reliable results, time and labor-intensive sample preparation and high cost *etc*. This article presents a fast, sensitive and quantitative method to determine sulfites in HMs using field asymmetric-wave ion mobility spectrometry (FAIMS) coupled with headspace bubbling method. The headspace air bubbling method is effective and efficient in generating stable SO_2 in gas phase for FAIMS analysis. It shows that sulfites with a concentration down to 1 mg/kg can be easily detected by this new method in 20 min, much shorter than those of current technologies. The limits of detection (LOD) and limits of quantification (LOQ) are 1 mg/kg and 3 mg/kg in HMs, respectively. The new method is of great significance to ensure medical safety and for HM production quality control.

Keywords: field asymmetric-wave ion mobility spectrometry (FAIMS); sulfur dioxide (SO_2); headspace bubbling; herbal medicines (HMs).

1. Introduction

Sulfites, commonly known as sulfur dioxide (SO_2) and inorganic sulfites that can be easily changed to SO_2, are a type of food additives and are also used as preservative, antioxidant and antibacterial agents in some food products.[1-3] However, over-ingestion of sulfites has been shown to be hazardous and harmful to humans. It causes allergic reaction and food intolerance symptoms. Sensitive individuals may also experience adverse reactions when they consume foods containing excessive sulfites.[4-6] Therefore, control and regulation of the use of sulfites in foods are extremely important for the safety of consumers. The sulfite contents in some foods are strictly controlled in some countries and by the international organizations such as, the European Union (UN), the United States Food and Drug Administration (FDA), the Japanese Food Hygiene Association (JFHA) and Chinese National Standard Management Committee (CNSMC).[7,8]

Recently, herbal medicines (HMs) have attracted many attentions for the treatment of chronic diseases, nutrition complement and healthcare, *etc*.[9] Since HMs are some kinds of plants that contain a large amount of water, often accompanied with microbe, fungus, and insects, they are difficult in preservation. Sulfur fumigation (SF) is widely used in HMs processing and preparation for better preservation in Asia.[10] Detailed investigations into sulfur fumigated raw materials have revealed some negative effects including harm to health by sulfite residues[11,12] and reduced bioactive compounds in HMs.[13-16]

Governments all over the world and international organizations have introduced the limits of sulfite residues in various HMs. In 2011, the regulations for sulfite residues in HMs have been introduced by China Pharmacopoeia Committee (CPC). The concentration of sulfite residues in eleven types of HMs, including *Radix Achyranthis Bidentatae, Radix Asparagi and Rhizoma*

Atractylodis Macrocephalae should not exceed 400 mg/kg, while others should not exceed 150 mg/kg. The South Korea Food and Drug Safety Agency (KFDA) has set the SO_2 residue to less than 30 mg/kg in two hundreds sixty seven types of HMs. The United States Food and Drug Administration (FDA) has required a clear sulfite warning label on food packages once the residual concentration in the food is 10 mg/kg or more.

The quantitative determination of SO_2 residue in HMs is a difficult and time-consuming process due to two reasons: HMs composition is very complex, and easily interferes with SO_2 analysis, and there exist various forms of sulfites in HMs by sulfur fumigation, making the extraction and measurement of SO_2 extremely difficult. Various methods for the determination of SO_2 concentration have been developed. Volumetric determination for sulfites has been introduced by the official institutions.[17,18] This method utilizes distillation of samples under acidic condition and then analyzes sulfites by iodine or acid-base titration. Although it is simple, and does not need expensive equipment, the inaccurate determination of titration end point and the complexity of sample matrix restrict its widespread application. Several other analytical techniques have also been attempted for the analysis of sulfites in HMs, such as electroanalytical methods,[19] flow injection analysis,[20-23] chemiluminescence determination,[24] ion chromatography (IC),[25,26] *etc*. These methods usually require time and labor consuming sample pretreatment and analytic solution preparation. Although the aforementioned methods have shown good sensitivity or selectivity, most of them cannot produce reliable results at the level around or below 10 mg/kg.[27] For other methods, the reproducibility is unsatisfactory and sample pretreatment requires complex and high-cost instruments. Therefore, there is an urgent need to develop sensitive, fast and low-cost methods or instruments for the determination of SO_2 in HMs for drug safety and

health.

This paper reports a new method for the direct determination of SO_2 in HMs using fast field asymmetric-wave ion mobility spectrometry (FAIMS) coupled with a headspace air bubbling method. The results demonstrate that the FAIMS has a high sensitivity to sulfites in HMs, and is able to detect sulfites in HMs down to 1 mg/kg with much shorter time than those of the current technologies. Also the procedure developed for sample preparation and measurement is simple, efficient and effective compared to the current ones.

2. Experimental

2.1 Chemical and materials

Sodium sulfite standard solution (1 mg/mL) was purchased from National Research Center for Certified Reference Materials (Beijing, China), sodium hydroxide, hydrogen peroxide (purity ⩾ 30%), ferrous sulfate, soluble starch and iodine volumetric solutions (0.01204 mol/L) were all purchased from Sinopharm Chemical Reagents Co. (Shanghai, China). Sulfuric acid (⩾98%) and sodium potassium tartrate were purchased from Aladdin industrial corporation (Shanghai, China). D-Mannitol, with a purity⩾96%, was purchased from Sigma-aldrich (Shanghai, China). All the chemicals and reagents were analytically pure, and were used directly without further purification. Ultrapure water was produced by a Millipore water purification system (Billerica, MA, USA).

Forty five kinds of herbal medicine raw materials were all purchased from the local pharmacy of Suzhou (Jiangsu, China). All samples were cut into pieces and grinded to make them in a powder form. They were stored at 4 ^{o}C before testing.

Solutions used were prepared as follows. A standard stock solution with a concentration of 1000 mg/L, equal to 500 mg/L of SO_2 solution. A 5.0 mg/L of the standard solution was prepared by

diluting the stock solution with D-mannitol solution. The purpose of adding D-mannitol in the stock solution is to prevent the oxidation of sodium sulfite. A sulfurous acid-free sulfuric acid solution was prepared by diluting the concentrated sulfuric acid solution with water to a concentration of 5% (V/V), and then adding a 0.25 mL of hydrogen peroxide solution and mixing it well, and finally adding 4 g of ferrous sulfate and mixing. The purpose of adding hydrogen peroxide is to oxidize traces of sulfurous acid in 5% sulfuric acid solution, while the added excess ferrous sulfate is to neutralize the hydrogen peroxide concentration which remains too high after the oxidation of sulfurous acid. 25 g of sodium potassium tartrate and 40 g of sodium hydroxide were dissolved in ultra-pure water to obtain a stock solution of 1 L as an alkaline extraction solution.

2.2 Instrumentation

The high-field asymmetric ion mobility spectrometer based on Ni^{63} ionization was developed by the authors based on the ultrafast MEMS-type FAIMS technology.[28] The radio-frequency (RF) dispersion field (DF) range was from 0 to 220 Td (1Td=?????). The compensation field (CF) was from -8.01 to 8.01 Td and the operating frequency was 25 MHz. Detection of SO_2 was operated in the negative mode, with each full range CF scan at any DF level taking 2 seconds. Standard SO_2 gas cylinder was purchased from Xundong Information Technology CO. LTD (Suzhou, China) for verification test with the SO_2 concentration of 1 μL/L (deviation was about 4%) in nitrogen. The chromatographic verification analysis was carried out in a GC coupled to a 5975C inert MSD with Triple-Aix detector (Agilent Technologies). Chromatographic separation was carried out with a GC-GasPro capillary column (30 m×320 μm, 0.32 μm thickness). GC/MS was used to verify the interference of complex sample matrix.

2.3 FAIMS analytical conditions

FAIMS separates different types of compounds based on the nonlinear field-dependence of mobility coefficients in a RF dispersion electric field.[29] The ion chemistry of Ni^{63} and nonlinear ion mobility in high field have been studied intensively, readers may refer ref.30 for details. In the ionization region, high energy primary electrons emitted from the ionization source, together with nitrogen, oxygen and water vapor in scrubbed air, initiating a series of reactions to produce the reactant ions ($H^+(H_2O)_n$ *and* $O_2^-(H_2O)_n$). Sample molecules (*M*) are ionized by charge transferring processes with reactant ions.

$$M + H^+(H_2O)_n \Leftrightarrow MH^+(H_2O)_n \Leftrightarrow MH^+(H_2O)_{n-x} + x(H_2O) \quad (1)$$

$$M + O_2^-(H_2O)_n \Leftrightarrow MO_2^-(H_2O)_{n-x} + x(H_2O) \quad (2)$$

Sulfur dioxide possesses a high electron affinity,[31] its characteristic peaks in FAIMS spectrum are expected to appear in the negative mode and would not be interfered by humidity variation too much. Fig. 1 shows the relationship between the ion current value and dew point. As can be seen from Fig. 1, the detected signal of 70 μg/L SO_2 from a standard solution is constant when the dew point is changed from -70 ^oC to -55 ^oC.

The schematic experimental setup is shown in Fig. 2. Zero air (Peak, UK) was scrubbed by molecular sieve and activated charcoal. Scrubbed air was then split into two flows by two mass flow controllers (MFC). The dew point of the flow was below -55 ^oC, monitored by a dew point sensor (Michell, UK). A sample introduction flow rate was 15 mL/min, and was connected to the sample reaction bottle (Gas/Liquid=1, V/V, with a total volume of 70 mL) to create bubbles. The diluted flow rate was set to 2.0 L/min. The pressure in the FAIMS analyzer was controlled at 1 atm.

2.4 Sample preparation and analysis

To prepare the extraction solution for HMs analysis, we followed the optimized procedure revealed in the literature.[32] A 1.0 g of HMs samples was placed in a 150 mL extraction bottle, and 100 mL extraction solution was added. The mixture was shaken in an ultrasonic bath for 15 min to extract sulfites. A certain volume (≤1.0 mL) of the supernatant was transferred into the headspace bottle. After that, a 5% of sulfuric acid solution was pumped into an automatic peristaltic pump to make up a total liquid volume of 35 mL. The headspace bottle was kept at 25 ^{o}C, and a magnetic stirrer was used for blending. The SO_2-containing gas was directly carried by air into the FAIMS system for analysis.

2.5 Theoretical considerations

SO_2 dissolved in the acidic solution exists in several forms, which is determined by the following equilibrium equations.

$$SO_2(gas) + nH_2O \Leftrightarrow SO_2 \cdot nH_2O \quad K_{HS} = \frac{[SO_2 \cdot nH_2O]}{P_{SO_2}} \tag{3}$$

$$SO_2 \cdot nH_2O \Leftrightarrow H^+ + HSO_3^- + (n-1)H_2O \quad K_{S_1} = \frac{[H^+][HSO_3^-]}{[SO_2 \cdot nH_2O]} \tag{4}$$

$$HSO_3^- \Leftrightarrow H^+ + SO_3^{2-} \quad K_{S_2} = \frac{[H^+][SO_3^{2-}]}{[HSO_3^-]} \tag{5}$$

Where K_{HS} is Henry's law constant of SO_2, P_{SO_2} is the partial pressure of SO_2 in the head space after the equilibrium is established. K_{S_1} and K_{S_2} are the dissociation constants for the first and second protons, that are temperature dependent. The three constants used in this work are summarized in Table 1. It is assumed that the reaction to produce SO_2 is instantaneous and thorough when high enough concentration of sulfuric acid is used. The ratio of

$\frac{[SO_3^{2-}] + [HSO_3^-]}{[SO_2(gas)] + [SO_2 \cdot nH_2O] + [SO_3^{2-}] + [HSO_3^-]}$ is thereby calculated in a 5% of sulfuric acid to be 1.38%. This value indicates that most of SO_2 in solutions exist in the form of $[SO_2 \bullet nH_2O]$

Equation 3 can be subsequently solved for certain concentrations of $[SO_2 \bullet nH_2O]$, which is equivalent to the concentration of sulfites in the solution. Table 2 shows a mapping of the sulfite concentration in the solution and the SO_2 in the headspace. The concentration of sulfuric acid, which provides most of protons in the solution, determines the concentration of $[SO_2 \bullet nH_2O]$ in the solution by equation 4 and 5, and partial pressure of SO_2 in the headspace at the end. The value of 5% of sulfuric acid is selected to keep the concentration of SO_2 in table 2 within the range from 0 to 23.45 nL/L, which is within the dynamic range of FAIMS analysis.

It is worth noting that the calculation is for the static headspace, in which the equilibrium partial pressure of SO_2 takes a certain time to be established. Because SO_2 is introduced into FAIMS dynamically, the equilibrium partial pressure of SO_2 needs to be maintained for a certain time for stable spectral analysis.

3. Results and discussion

3.1 Comparison of sample introduction methods

It takes tens of seconds to collect the DF: CF spectrum, which is used to identify characteristic DF: CF peaks of SO_2. For quantitative analysis, the SO_2 concentration must be stable in the flow during the spectral analysis. Three methods were tried for the SO_2–containing gas flow to be introduced from the headspace of the reaction bottle to the FAIMS detector, with the results shown in Fig. 3-5.

First, SO_2 in the headspace is dynamically swept by the sample flow from the solution surface

as shown in Fig. 3a. Assume dynamic equilibrium is established for SO_2 between the gas and solution in the headspace, then the concentration in the gas phase is dependent on the surface area, flow rate, temperature and pressure. At an optimal flow rate, the detected SO_2 concentration (donated as FAIMS ion current) reaches a peak after several minutes and quickly diminishes when the SO_2 concentration exhausts, as shown in Fig. 3b. Although quantitative analysis can be achieved with this method, the misalignment of ion peaks at different concentrations along the time axis results in the compression on certain concentration range on the dynamic curve, hence the inaccurate determination of SO_2 concentration. In addition, the turbulence brought by the sample flow on the solution surface also produces fluctuation of ion current, making the measurement difficulty.

The second method is to utilize liquid flow to replace the equilibrium gas phase flow as shown in Fig. 4c. The liquid flow was purged with 5% of sulfuric acid by a peristaltic pump to maintain the pH value of the solution. Once the headspace equilibrium is established, sulfuric acid is purged into the bottle to increase the solution level as well as to extrude the headspace gas, while keeping the headspace concentration constant. Fig. 4d shows the relation between the ion current and time with ion concentration as a variable. By adjusting the liquid flow rate, a plateau instead of a peak in ion current can be obtained, which provides a stable time window for spectral analysis. However, the use of sulfuric acid may put the instrument and operator at risk, thus it is not recommended for practical use.

A new air bubbling method has been developed by the author as shown in Fig. 5e. By optimizing the air flow to create small gas bubbles, a gas-liquid equilibrium can be established for both the solution and the gas phase. We have estimated the ion concentrations in the gas phase that

are consistent with the theoretical calculation. Fig. 5f shows the ion current profiles at various SO_2 concentrations. The sample flow was optimized to be 15 mL/min which is a trade-off result with bubble size, dynamic range of SO_2 concentration and the humidity. The bubbles have an average diameter of 1 mm, measured by a high speed video camera. The sample flow was then mixed with the carried air flow of 2.0 L/min immediately before entering the FAIMS detector. The second and fourth row of Table 2 shows the calculated concentrations of SO_2 in the total flow described above.

To explore the dynamic range of SO_2 in the FAIMS instrument as well as to verify the calculated values in Table 2. Air flows from gas cylinders with different known SO_2 concentrations were analyzed by FAIMS, and it was demonstrated that FAIMS can measure the SO_2 concentration in the range from 0 to 20 nL/L accurately and dynamically. Fig. 6 compares the dynamic ion current curves of SO_2 from gas cylinders and those obtained through bubbling method. Both show a similar curve, but the bubbling method produces lower concentrations than those obtained by the cylinders. The deviation between these two sets of results is mainly caused by the deviation of the SO_2 itself in the ideal gas (about 2.4%) [33] and the concentration fluctuation from the gas cylinders (about 4%).

3.2 Experimental verification of sulfites forms in HMs

As can be seen from the literature,[32, 34-36] sulfites in foods exist in both the combined forms (reversible and irreversible) and free forms. Sulfites can be transferred into a reversibly combined form by aldehyde, ketone, 2-ketoglutaric acid, pyruvic acid, glucose, mannose and fructose[37]. Irreversibly combined form sulfites generally will not dissociate in human body, therefore they are not harmful to human health[38].

Generally, the acid treatment is used for measuring the free form sulfite, and while the alkali treatment is used to determine total sulfites concentration.

In order to verify the efficiency of the extraction process for both free and combined forms, recoveries were investigated by comparing the FAIMS results with those by the titration method for both the prepared solution and real HM samples.

To prepare the standard sulfites solution in a combined form, the reagents of acetaldehyde, mannose, and pyruvic acid were added into the standard pre-prepared sulfite solution for measurements. Table 3 is the comparison of the recovery results obtained by the acid extraction and the alkaline extraction methods. It shows that there is no difference in the recovered sulfites concentrations if the solutions only contain sodium sulfite, and the recoveries obtained by both method are all above 90%. When sodium sulfite is converted to the combined form by adding either mannose, pyruvic acid or acetaldehyde, the recoveries are only 10.3%, 34.2% and 0.19%, respectively using the acid extraction method, while that are 82.7%, 79.8% and 62.9%, respectively using the alkaline extraction method.动词要修改为过去时态。

Sample *Radix Angelicae Sinensis* was prepared by both the acid and alkaline extractions, and analyzed by two titration analysis methods and FAIMS method. The results are summarized in Table 4. Obviously, the alkaline extraction shows significantly more sulfites in the solutions than those by the acid extraction owing to the transformation of the combined form of sulfites into the free form one.

3.3 The possible gas impurities in FAIMS analysis

Carrier gas may contain some impurities that will affect the determination of SO_2. To clarify possible impurities and their effects on the determination of SO_2 by FAIMS analysis, GC/MS

was used to investigate impurities in the headspace gas species.

The solution of selected HMs was prepared by the same procedure for the FAIMS analysis described above and the headspace gas was collected and injected into GC/MS by a GC microsyringe. The GC/MS analyses were operated under the following conditions: Helium was used as the carrier gas at a flow rate of 1.3 mL/min with split (1:10) injection. The temperature of the injection port and the detector were 200 ^{o}C and 230 ^{o}C, respectively. The oven temperature was set at 40 ^{o}C initially (6 min holding), was then ramped up to 230 ^{o}C at a rate of 20 ^{o}C/min (6 min holding). The total time used for one GC run was about 24 min. The full scan mode was used for qualitative analysis.

Only four peaks at the retention time of 0.878, 0.896, 1.413 and 7.608 min were found in the total ion chromatography (TIC) chromatogram as shown in Fig. 7a. The peaks at 0.878 and 0.896 min correspond to the N_2 and O_2, respectively and the peak at 1.413 min is CO_2. To clarify the peak at 7.608 min, it was further analyzed by the mass spectrum with the result shown in Fig. 7b. Fig. 7c is the NIST-library mass spectrum for SO_2. Comparison of Fig. 7b and 7c clearly shows that this signal peak is indeed the SO_2 with a mass in the range of 20～500 Da. The ion with m/z of 64 is attributed to the SO_2 molecule with one electron lost (one positively charged molecule). The experiments showed there is no other impurity in the carrier gas except for clean carrier gas (air).

3.4 Method evaluation

Before starting the measurement of SO_2 in HMs, a relationship between the real SO_2 concentration in solution and that determined by FAIMS measurement was established, so that it can be used to determine SO_2 concentration in HMs. This was done by using the standard

solution containing various sodium sulfite concentrations. Fig. 8 shows the dependence of FAIMS ion current on SO_2 concentration in the standard solution. The SO_2 concentration in the sulfite solution was in the range of 0~250 μg/L, corresponding to the gas phase concentration 0~20.50 nL/L in the FAIMS headspace. The relative standard deviation (RSD) is 4.46%. The limit of detection (LOD) of SO_2 calculated based on a signal-to-noise ratio of 3:1 is 1 mg/kg. The limit of quantification (LOQ) is 3 mg/kg which is defined as three times the LOD.

In order to verify the recoveries of the alkaline solution extraction combined with headspace air bubbling method, we selected *Rhizoma Atractylodis Macrocephalae*, *Rhizoma Dioscoreae*, *Rhizoma Gastrodiae*, *Radix Trichosanthis* to evaluate the extraction efficiency. The result verified the applicability of the proposed method.

3.5 Analysis of HMs

Using the optimal conditions determined above, we have successfully applied the FAIMS technique coupled with headspace air bubbling method for the quantitative analysis of SO_2 in HMs. An alkaline extraction solution, a 5% of sulfuric acid solution, a standard reaction solution (5% of sulfuric acid reacted with sodium sulfite solution) and a sample reaction solution (5% of sulfuric acid reacted with *Radix Angelicae Sinensis* sample extraction solution) were used. By varying DF, a characteristic CF spectral set can be obtained for chemical identification with the results shown in Fig. 9a-9d. Characteristic SO_2 spectra are shown in Fig. 9c and 9d. For quantitative analysis, one specific DF spectrum was used for the extraction of the current value. Fig. 9a1-9d1 show the results for the above solutions, correspondly, scanned at DF of 105 Td. Scan-lines from Fig. 9a1-9d1 were combined and are shown in Fig. 9e. The ion current peak of SO_2 appears at -0.876 Td (Curve c and d) free from interference.

Forty five kinds of HMs samples purchased from the local pharmacy were prepared to evaluate the developed method. Results obtained from FAIMS, CPC, AOAC and IC methods (The sample extraction process was the same as the optimized monier-williams method) are shown in Table 5. SO_2 was detected from twenty out of forty five kinds of HMs and among them, the SO_2 concentration from eighteen kinds of HMs exceeds the legal limit set by Chinese Authorities. Some samples such as *Flos Lonicerae, Fructus Citri Sarcodactylis, Radix Achyranthis Bidentatae, Radix Angelicae Sinensis, Rhizoma Atractylodis Macrocephalae, Radix Codonopsis,* contain excessive amounts of SO_2 in the range of XX~XX. The results indicate that sulfur fumigation for HMs preservation is a severe problem in China, and actions must be taken to reduce its impact on human health. As can be seen from Table 5, the results obtained from CPC and AOAC methods are consistent with each other. The ion chromatography results show a large deviation from others, while, the FAIMS analysis results for some HMs are smaller than those obtained from CPC and/or AOAC methods. It is speculated that in these HM samples, reversibly combined sulfite is rare. Meanwhile, acid and reductive substances vaporized from the sample solutions might result in higher titration values obtained by AOAC and CPC methods respectively.

4. Conclusions

This paper presented a new method to measure SO_2 in HMs by high field asymmetric-wave ion mobility spectrometry coupled with headspace air bubbling method. The obtained results were compared with those by currently used methods. The results demonstrated that the FAIMS method can detect SO_2 with a concentration down to 1 mg/kg in HM samples readily. In addition, the headspace air bubbling sample introduction method was demonstrated to have great compatibility with the FAIMS analysis, particularly the uniform sample flow generation. The results

demonstrated that FAIMS is a reliable method for fast, sensitive and quantitative determination of SO_2 in HMs. The method is of great significance to ensure medical safety and for HMs production quality control, thus it has a great potential for applications in many in-situ and rapid analytical fields.

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Figure captions

Fig. 1 The influence of humidity change.

Fig. 2. Schematic experimental setup for headspace bubbling -FAIMS analysis.

Fig. 3. Schematic diagram of headspace for dynamically sweep (a) and time-dependent profiles for various concentrations of SO_2 in solutions (b).

Fig. 4. Schematic diagram of static headspace for liquid flow purge (c) and time-dependent profiles for various concentrations of SO_2 in solutions (d).

Fig. 5. Schematic diagram of headspace bubbling (e) and time-dependent profiles for various concentrations of SO_2 in solutions (f).

Fig. 6. Comparison of theoretical calculation and actual measurement of SO_2. The continuous solid line is the calculated results by the standard solution. The continuous dotted line is the measured results by the gas cylinder.

Fig. 7.The GC/MS verification (a) is the total ion chromatogram (TIC); (b) is the mass spectrum of the peak at 7.608 min in the chromatogram; and (c) is the mass spectrum of SO_2 (NIST database).

Fig. 8. The ion current value measured at 4 min as a function of SO_2 concentration in 35 mL solutions.

Fig. 9. The spectrogram of the alkaline extraction solution (a), 5% of sulfuric acid solution (b), standard reaction solution(c), and sample reaction solution (d). The spectrogram at fixed E/N =105 Td for above four solutions (a1-d1). (e) is the combination of scan-lines at E/N =105 Td from (a) to (d), denoted in the same letter.

Figures

Fig. 1

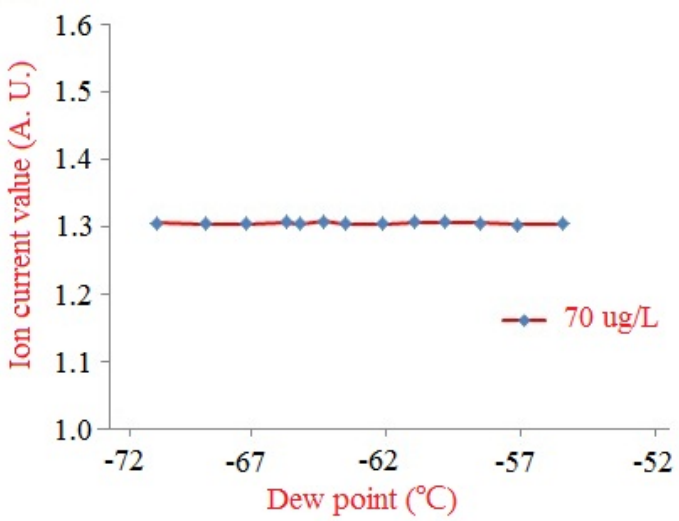


Fig. 2

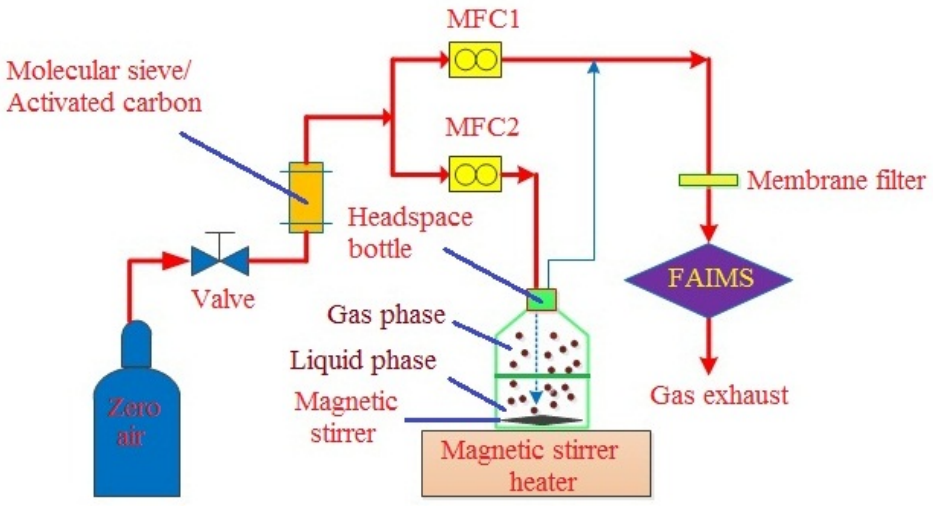


Fig. 3

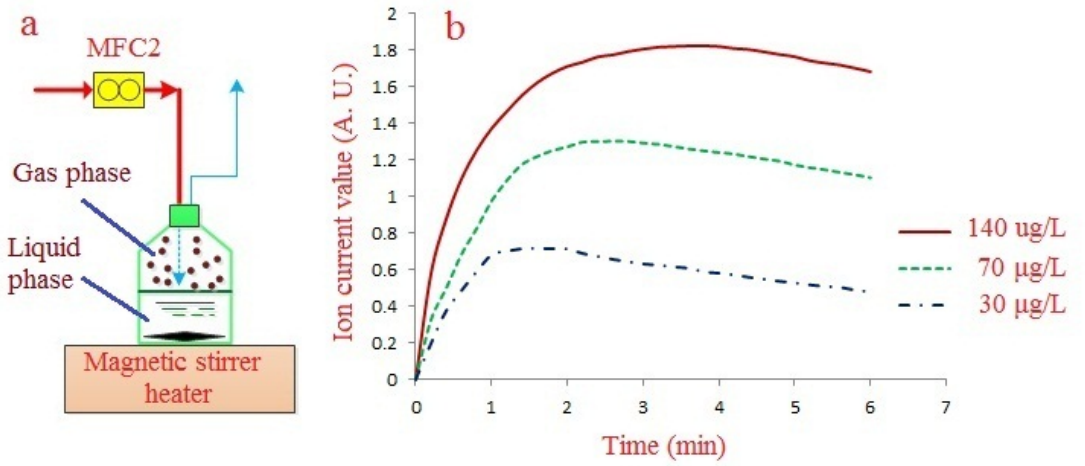

a
MFC2
Gas phase
Liquid phase
Magnetic stirrer heater
b
Ion current value (A. U.)
Time (min)
140 ug/L
70 µg/L
30 µg/L

Fig. 4

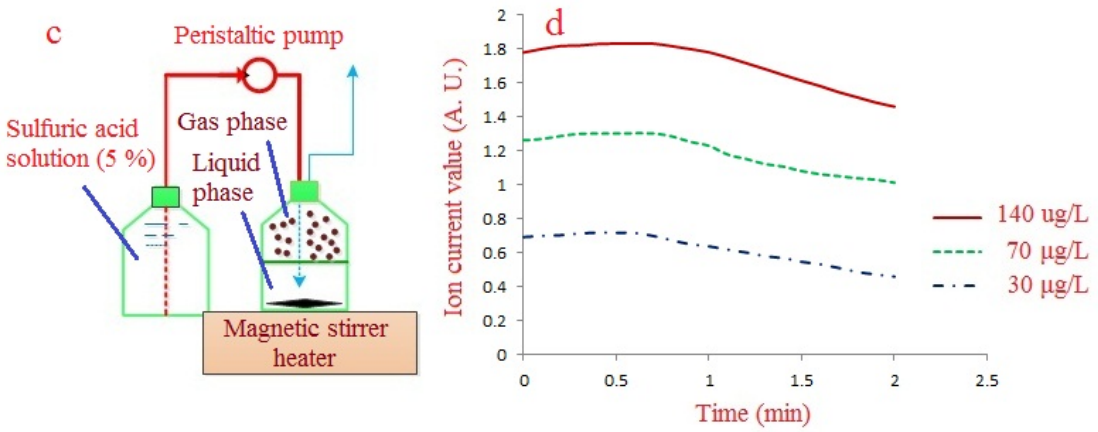

c
Peristaltic pump
Sulfuric acid solution (5 %)
Gas phase
Liquid phase
Magnetic stirrer heater
d
Ion current value (A. U.)
Time (min)
140 ug/L
70 µg/L
30 µg/L

Fig. 5

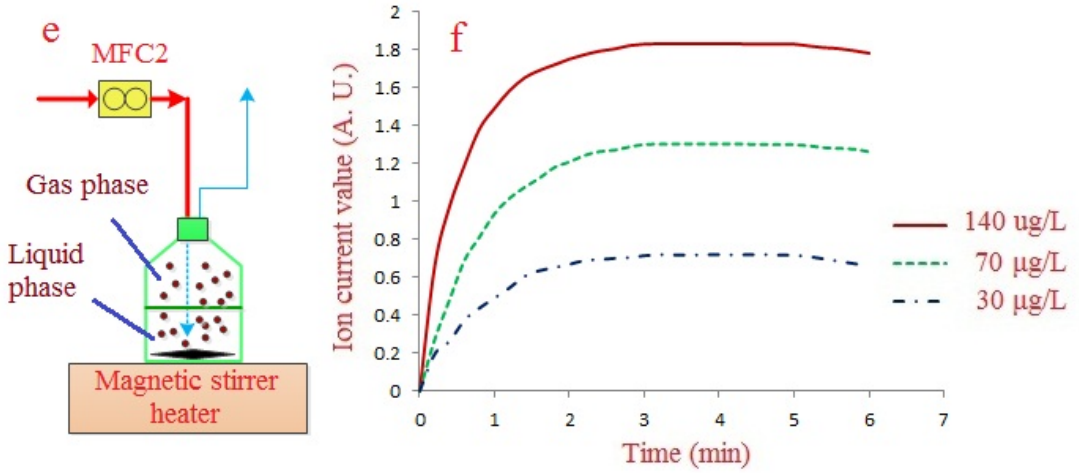

e
MFC2
Gas phase
Liquid phase
Magnetic stirrer heater
f
Ion current value (A. U.)
Time (min)
140 ug/L
70 µg/L
30 µg/L

Fig. 6

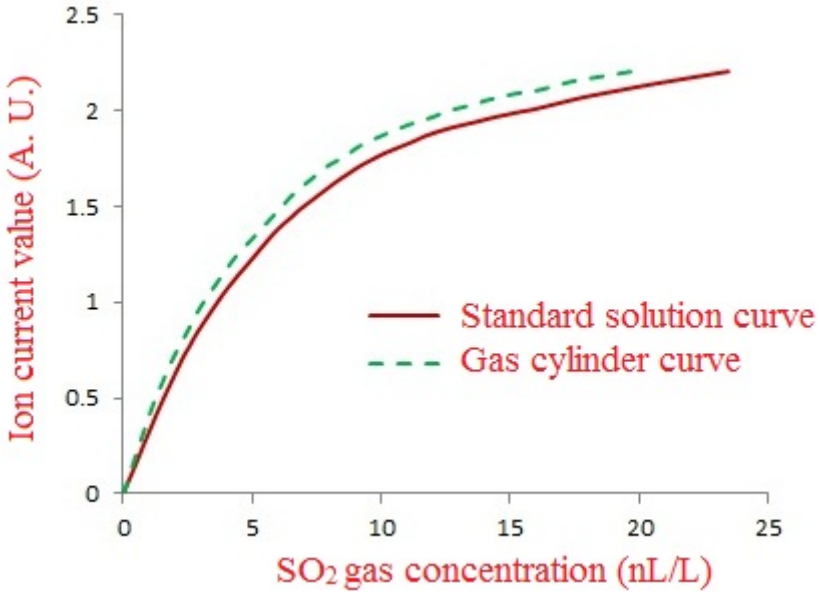

Ion current value (A. U.)
SO2 gas concentration (nL/L)
Standard solution curve
Gas cylinder curve

Fig. 7

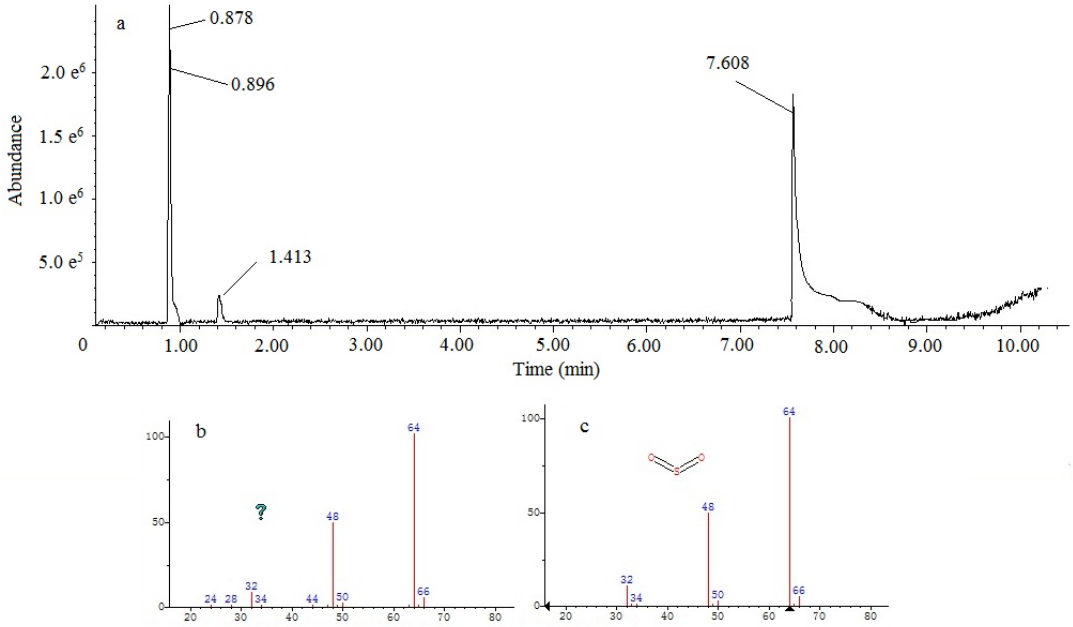

a
0.878
0.896
1.413
7.608
Abundance
2.0 e6
1.5 e6
1.0 e6
5.0 e5
0
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
10.00
Time (min)
b
c
100
50
0
64
48
32
66
50
34
24
28
44
20
30
40
50
60
70
80

Fig. 8

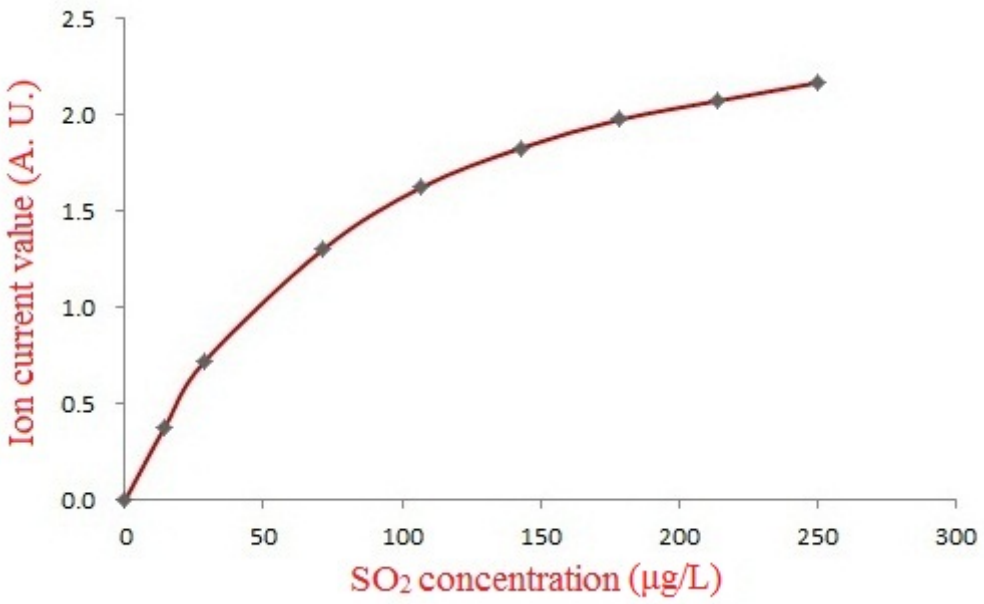
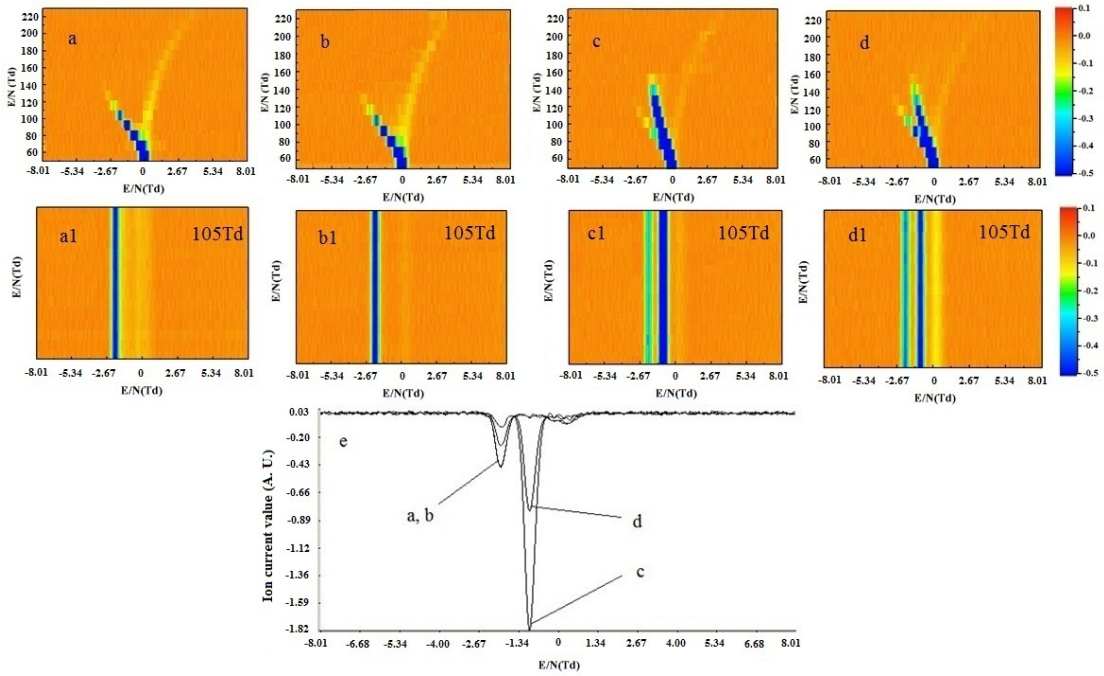

Ion current value (A. U.)
2.5
2.0
1.5
1.0
0.5
0.0
0
50
100
150
200
250
300
SO2 concentration (μg/L)

Fig. 9


a
b
c
d
a1
105Td
b1
105Td
c1
105Td
d1
105Td
E/N(Td)
e
a, b
d
c
Ion current value (A. U.)

Tables

Table 1 Constants used in the SO_2 equilibrium calculation (298K, atmosphere)

K_{HS}	K_{S_1}	K_{S_2}
1.2496	0.01326	6.44e-8

Table 2 Comparation of the gas/liquid distribution for theoretical calculation and the standard gas cylinder detection

SO_2 in solutions (μg/L)	0	14.3	28.6	71.4	107	143	214	250	286					
SO_2 in headspace gas phase [a] (nL/L)	0	1.173	2.345	5.855	8.774	11.73	17.53	20.50	23.45					
ICV[b] of solutions (A. U.)	0	0.379	0.719	1.363	1.675	1.869	2.061	2.138	2.205					
SO_2 in gas cylinder (nL/L)	0	1.00	2.50	3.00	5.00	6.00	7.50	8.00	10.0	12.0	14.0	16.0	18.0	20.0
ICV of standard gas (A. U.)	0	0.407	0.872	0.987	1.332	1.478	1.666	1.718	1.868	1.976	2.051	2.104	2.167	2.211

[a] Gas/Liquid distribution ratio is 0.0317. [b] Ion current value.

Table 3 The extraction comparative analysis results of free and combination form in sodium sulfite solutions

The solvent type of standard sodium sulfite solution.	CPC[a] Direct acid distillation	AOAC[b] Direct acid distillation	Extraction solution.	FAIMS analysis results for	Recoveries (%)/ RSD (%), n=6

Concentration: 5mg/L.	extraction	extraction	ICV. (A. U.)		
0.2% of mannitol	84.8%	84.2%	1[c]	1.829	92.5/1.74
			2[d]	1.821	90.2/2.98
0.1% of mannose	76.9%	75.8%	1	0.212	10.3/4.56
			2	1.649	82.7/2.21
0.1% of pyruvic acid	72.7%	72.2%	1	0.591	34.2/4.27
			2	1.594	79.8/2.67
0.1% of acetaldehyde	58.1%	58.6%	1	0.080	0.19/9.96
			2	1.409	62.9/6.53

[a] Chinese Pharmacopoeia Committee method; [b] Optimized Monier-Williams method; [c] 1.5% (W/V) of tartaric acid solution; [d] alkaline extraction solution.

Table 4 Comparison of different methods used to measure of SO_2.

Sample	Detection method	Pretreatment	Results (mg/kg)	Total analysis time	RSD, n=3 (%)
Radix Angelicae Sinensis	CPC[a]	Direct acid distillation extraction	1.03e^3	>40 min	6.66
	AOAC[b]		1.02e^3	>120 min	4.39
	Headspace Bubbling FAIMS	Alkaline solution extraction	2.11e^3	20 min	2.84
	CPC	Alkaline solution extraction - acid distillation extraction	1.64e^3	>60 min	5.19
	AOAC		1.55e^3	>140 min	4.28

[a] Chinese Pharmacopoeia Committee method; [b] Optimized Monier-Williams method.

Table 5 Comparison of different methods for the determination of SO_2 in HMs

Samples	Results			
	CPC[a] method, mg/kg/RSD, %, n=3	AOAC[b] method, mg/kg/RSD, %, n=3	IC[c] method, mg/kg/RSD, %, n=3	Headspace Bubbling-FAIMS, mg/kg/RSD, %, n=3
Bulbus Fritillariae Cirrhosae	$4.20e^2$/1.46	$6.12e^2$/1.08	$1.12e^3$/3.10	$1.06e^3$/4.17
Bulbus Lilii	$1.86e^2$/2.34	$4.50e^2$/8.35	$7.84e^2$/5.01	$8.35e^2$/2.18
Cortex Mori	$7.60e^2$/5.91	$4.37e^2$/3.94	-	$4.11e^2$/3.98
Cortex Moutan	-	$1.31e^2$/5.55	$3.98e^2$/1.65	70.0/3.05
Flos Lonicerae	$2.94e^3$/3.16	$3.13e^3$/2.02	-	$3.12e^3$/3.66
Fructus Citri Sarcodactylis	$2.34e^3$/3.78	$2.05e^3$/4.09	$3.368e^3$/7.03	$2.08e^3$/1.07
Fructus Lycii	$2.22e^2$/6.91	99.3/4.09	$3.17e^2$/2.38	$1.11e^2$/8.01
Radix Achyranthis Bidentatae	$2.98e^3$/5.51	$2.63e^3$/7.83	-	$2.62e^3$/4.44
Radix Adenophorae	$7.83e^2$/2.49	$8.19e^2$/3.44	-	$7.28e^2$/1.67
Radix Angelicae Sinensis	$1.01e^3$/2.18	$8.73e^2$/2.77	$1.80e^3$/2.90	$1.98e^3$/2.45
Radix Codonopsis	$1.97e^3$/1.83	$2.30e^3$/0.81	$2.48e^3$/4.01	$1.96e^3$/1.77
Radix Paeoniae Alba	$5.68e^2$/2.89	$4.75e^2$/1.73	$1.02e^3$/6.22	$4.79e^2$/3.39
Radix Panacis Quinquefolii	$6.76e^2$/4.52	$7.80e^2$6.25	-	$9.43e^2$/0.83
Radix Platycodonis	$1.56e^2$/3.43	28.5/1.71	-	61.8/2.98
Radix Pseudostellariae	$8.31e^2$/3.18	$9.48e^2$/6.05	$1.07e^3$/3.30	$9.52e^2$/4.98
Radix Puerariae	$5.11e^2$/2.17	$5.99e^2$/2.64	-	$6.86e^2$/7.88

Radix Trichosanthis	$8.75e^2/1.43$	$1.02e^3/2.69$	-	$9.06e^2/2.72$
Rhizoma Atracylodis Macrocephalae	$1.56e^3/2.71$	$1.50e^3/1.21$	$1.91e^3/3.97$	$1.55e^3/2.25$
Rhizoma Bletillae	$3.91e^2/3.85$	$2.62e^2/1.73$	$5.34e^2/5.28$	$4.54e^2/1.99$
Rhizoma Dioscoreae	$7.72e^2/8.99$	$7.10e^2/4.21$	-	$5.86e^2/6.15$
Rhizoma Gastrodiae	$2.45e^2/2.10$	$1.33e^2/5.00$	-	$1.53e^2/5.76$
Rhizoma Imperatae	-	89.5/5.09	$2.50e^2/2.76$	$3.85e^2/2.94$
Rhizoma Smilacis Glabrae	$2.18e^2/3.66$	$1.34e^2/1.79$	$4.16e^2/2.16$	$4.00e^2/9.50$
Semen Armeniacae Amarum	$2.87e^2/6.06$	$1.00e^2/3.03$	$1.20e^2/2.98$	$1.95e^2/3.77$

[a] Chinese pharmacopoeia Committee method; [b] Optimized Monier-Williams method. [c] Ion chromatography method. – Not be measured.